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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/072,525	02/05/2002	Karla Robotti	10011206	2898

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/072,525	ROBOTTI, KARLA	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9,14-21,24,26-56,58 and 59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *44* is/are allowed.

6)☒ Claim(s) *9,14,15,28-32,37-40,45-56,58 and 59* is/are rejected.

7)☒ Claim(s) *1-6,16-21,24,26,27,33-36 and 41-43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's fourth submission after final filed on 8/19/05 has been entered.

Claims 1-6, 9, 14-21, 24, 26-56 and 58-59 are pending in the present application, and they are examined on the merits herein.

Response to Arguments

The rejection under 35 U.S.C. 112, second paragraph, is withdrawn in light of Applicant's assertion that the term "the porous inorganic material is formed *in situ*" is clear and it means that the matrix is formed as part of the microanalytical device recited in the preamble of the claims (see Appeal Brief filed on 8/19/05, pages 8-9).

The rejection under 35 U.S.C. 103(a) as being unpatentable over Dunn et al. (U.S. Patent No. 5,200,334) in view of Reetz et al. is withdrawn in light of Applicant's assertion that the term "the porous inorganic material is formed *in situ*" means that the matrix is formed as part of the microanalytical device and not in any reaction vessel (see Appeal Brief filed on 8/19/05, page 14, second and third paragraphs).

Claim Objections

Claims 1, 9 and their dependent claims are objected to because of the term "in step (b)". This is because the steps of the recited methods are not labeled. Appropriate correction is required.

Claim Rejections - 35 USC § 102

Claims 45-48, 51, 55-56 and 58-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Lochhead et al. (US 6,039,897). ***This is a new ground of rejection.***

Lochhead et al disclose a Micro-molding in capillaries (MIMIC) process for fabricating micronscale structures or devices, said method comprises the steps of: providing a micro-mold having a plurality of non-communicating independent channels and having a plurality of reservoirs for receiving a micro-molding fluid each of which reservoirs communicates with a channel, introducing a micro-molding fluid into the micro-mold reservoirs filling said communicating channels; and solidifying the fluid in the micro-mold and removing the elatomeric master (see abstract). The used micro-molding fluid is a sol that can comprise a variety of biologically active molecules including proteins, enzymes, antibodies, antigens and nucleic acid which bind to, or interact with analytes including other biologically active molecules (col. 6, lines 9-62). Micro-molding fluids can further comprise whole biological cells and/or cell fractions (col.6, lines 46-49). The reservoirs and the connected channels are independent so that multiple materials can be patterned in a single step by introducing different micro-molding fluids into different reservoirs (col. 4, lines 38-42). Lochhead et al further teach that primary uses for the devices created by this process are in sensor, waveguide and

integrated optics applications (col. 4, lines 24-26; col. 9, lines 9-36). Lochhead et al further teaches an exemplified fluid channel that is an element of a micro-fluidic chemical analysis system with appropriate means for fluid sample introduction and a means for detecting indicator response to a particular analyte that may be present in fluid passed through the micro channel (see Fig. 5, and col. 9, lines 37-62). The channel is optically accessible through an optically transparent cover for detection of dye fluorescence (col. 9, lines 37-62). Due to the presence of multiple fluid channels, the micro-fabriacated devices of Lochhead et al. are capable of performing high throughput screening of samples. Additionally, the arrangement of multiple independent fluid channels in a microfabricated device can also be considered to be a form of a microarray (see Fig. 1). It is also noted that the term "monolith" means a solid-like body in visible one piece, and may be from several um in size to greater than tens of mm in size and beyond (page 10, lines 27-28).

Accordingly, the teachings of Lochhead et al meet all the limitation of the instant claims. Therefore, the instant claims are anticipated by US 6,039,897.

Claim Rejections - 35 USC § 103

Claims 9, 14-15, 28-32 and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunn et al. (U.S. Patent No. 5,200,334) in view of Reetz et al. (Biotechnology and Bioengineering, Vol. 9:527-534, 1996) and Lochhead et al. (US 6,039,897). ***This is a new ground of rejection.***

Dunn et al. teach a process for the production of a porous, transparent sol-gel glass containing an alcohol sensitive active biological material entrapped therein comprising: (a) forming a single phase sol by mixing a metal alkoxide in a non-alcoholic medium comprising water and an acid catalyst in a container exposed to ultrasonic energy, the mixture having a pH not greater than about 2; (b) removing the ultrasonic energy and raising the pH of the sol to about 5 to 7 by the addition of a buffering agent; c) adding an alcohol sensitive active biological material to the buffered sol; (d) forming a gel and allowing the gel to age; and (e) allowing at least a portion of the water in the gel to evaporate so that the volume of the product produced in step (d) is decreased and the active biological material is trapped in a monolith of the gel having a reduced volume (see abstract, Fig. 1 and claim 1). Although the exemplified method utilizes tetramethylorthosilicate (TMOS), and proteins (e.g., RNase A, proteases, hemoglobin, cytochrome c, metal ion binders, see col. 3, lines 38-59 and Table 1) as active biological materials, however other silicon alkoxides such as tetraethylorthosilicate (TEOS) and other active silicon compounds as well as other metal alkoxides (not limited to aluminium, titanium, zirconium, vanadium, sodium, calcium and boron or **combinations thereof**) can be used (col. 2, line 60 continues to line 10 of col. 3). Dunn et al. further teach that **it would be highly advantageous to encapsulate enzymes in a porous, transparent glass structure, such as structures prepared by the sol-gel process. Such an encapsulation would be significantly easier to minaturize and would be far less cumbersome and far more reliable than membrane encapsulating systems**. Furthermore, enzyme encapsulation within a transparent glass structure

would allow for the monitoring of many enzymatic reactions by using simple, photometric monitoring systems (col. 1, lines 27-36); and because of the light transmission characteristics of the glasses, UV, IR and visible light optical spectroscopy as well as fluorescence, luminescence, absorption, emission and reflection techniques are all suitable for quantitative and/or qualitative monitoring of chemical changes produced by the sol-gel glasses with entrapped enzymes (col. 4, lines 49-56).

However, Dunn et al. do not specifically teach a method wherein the sol comprises a tetralkyl orthosilicate and a silane, wherein the silane is substituted with a C_8-C_{24} alkyl group and substituted with at least two leaving groups selected from the group consisting of OR and halo; or for immobilizing a biological molecule in a porous inorganic matrix incorportated into a microanalytical device even though they teach that encapsulating enzymes by the sol-gel process would be significantly easier to miniaturize and would be far less cumbersome and far more reliable than other encapsulating systems.

However, at the filing date of the present application Reetz et al. already taught that lipase activity for lipases entrapped in sol-gels prepared from a mixture of tetramethoxysilane (TMOS) and alkyltrimethoxysilanes $Rsi(OCH_3)_3$ **was dramatically enhanced** with increasing amount and alkyl chain length of the hydrophobic silanes, including the alkyl group C_{18} (page 529, right-handed column, first complete paragraph and Figure 1). Additionally, Lochhead et al disclose a Micro-molding in capillaries (MIMIC) process for **fabricating micronscale structures or devices for use in sensor, waveguide and integrated optics applications** using a micro-molding fluid

that is a sol that can comprise a variety of biologically active molecules including proteins, enzymes, antibodies, antigens and nucleic acid which bind to, or interact with analytes including other biologically active molecules (see at least col. 6, lines 9-62). Lochhead et al further teaches that the potential for rapid analysis and portability makes microfabricated devices attractive for applications ranging from remote chemical sensing to medical diagnostics (col. 1, lines 18-22).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the method taught by Dunn et al. by further introducing a substituted silane in the process of immobilizing an enzyme, particularly a lipase, in a porous inorganic matrix in light of the teachings of Reetz et al. due to the stabilizing effect on entrapped lipase by increasing amount and alkyl chain length of the hydrophobic silanes; as well as for incorporating the immobilized biological molecule in a porous inorganic matrix into a microanalytical device in light of the above teachings of Lochhead et al. The modified method as the result of the combined teachings of Dunn et al., Reetz et al. and Lochhead et al. would be indistinguishable from the presently claimed method.

An ordinary skilled artisan would have been motivated to carry out the above modifications because increasing amount and alkyl chain length of the hydrophobic silanes, including the alkyl group C_{18} enhance lipase-doped sol-gel as taught by Reetz et al., coupled with the advantages offered by microfabricated devices (e.g., rapid analysis and portability) using the sol-gel process for use in sensor, waveguide and integrated optics applications as taught by Lochhead et al.

An ordinary skilled artisan would have a reasonable expectation of success based on the teachings of Dunn et al, Reetz et al, and Lochhead et al, as well a high level of skill of an ordinary skilled artisan in the art.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 46-47, 49-50 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lochhead et al. (US 6,039,897) in view of Avnir et al. (U.S. Patent No. 5,300,564; IDS) and Swedberg et al. (U.S. Patent No. 6,240,790). ***This is a new ground of rejection.***

Lochhead et al disclose a Micro-molding in capillaries (MIMIC) process for fabricating micronscale structures or devices, said method comprises the steps of: providing a micro-mold having a plurality of non-communicating independent channels and having a plurality of reservoirs for receiving a micro-molding fluid each of which reservoirs communicates with a channel, introducing a micro-molding fluid into the micro-mold reservoirs filling said communicating channels; and solidifying the fluid in the micro-mold and removing the elatomeric master (see abstract). The used micro-molding fluid is a sol that can comprise a variety of biologically active molecules including proteins, enzymes, antibodies, antigens and nucleic acid which bind to, or interact with analytes including other biologically active molecules (col. 6, lines 9-62). Micro-molding fluids can further comprise whole biological cells and/or cell fractions (col.6, lines 46-49). The reservoirs and there connected channels are independent so

that multiple materials can be patterned in a single step by introducing different micro-molding fluids into different reservoirs (col. 4, lines 38-42). Lochhead et al further teach that primary uses for the devices created by this process are in sensor, waveguide and integrated optics applications (col. 4, lines 24-26; col. 9, lines 9-36). Lochhead et al further teaches an exemplified fluid channel that is an element of a micro-fluidic chemical analysis system with appropriate means for fluid sample introduction and a means for detecting indicator response to a particular analyte that may be present in fluid passed through the micro channel (see Fig. 5, and col. 9, lines 37-62). The channel is optically accessible through an optically transparent cover for detection of dye fluorescence (col. 9, lines 37-62). Due to the presence of multiple fluid channels, the micro-fabriacated devices of Lochhead et al. are capable of performing high throughput screening of samples. Additionally, the arrangement of multiple independent fluid channels in a microfabricated device can also be considered to be a form of a microarray (see Fig. 1). It is also noted that the term "monolith" means a solid-like body in one piece, and may be from several um in size to greater than tens of mm in size and beyond (page 10, lines 27-28).

Lochhead et al. does not teach explicitly a method of using a microanalytical device comprising a sol-gel in the form of a microcolumn for separation/detection of an analyte sample.

However, at the filing date of the present application, Avnir et al already teach obtaining a chemical interaction between at least one reagent trapped in sol-gel glass by doping it with the reagent, and diffusible solutes or components in an adjacent liquid

or gas phase. The reagents, the solutes and the components can be any organic or inorganic compounds or materials of biological origin including enzymes (see abstract). Avnir et al further teach that the doped sol-gel glass can be in any shape suitable for the test, for example, it can have the shape of rods, discs, cubes, sieves, powder or thin films coating conventional glass plates or any other inert solid support (col. 3, lines 20-24). Avnir et al also teach that the doped sol gel glasses can be used for all chromatographic purposes including liquid, gas and thin layer chromatography. The extraction or separation is performed by passing the solution through columns made from appropriately doped sol gel material (col. 3, lines 445-52).

Swedberg et al also teach a high-throughput microanalysis device having a plurality of sample processing compartments for use in analysis of small and/or macromolecular and/or other solutes in the liquid phase (see abstract). The microstructures in the microanalysis device include sample separation means that include electochromatographic separations performed in columns or microcapillary format (col. 6, line 61 continues to lines 49 of col. 7). Swedberg et al also teach that the microanalysis device is interfaced with any analytical detection means well known in the art, such as UV/Vis, Near IR, fluorescence, refractive index (RI), Raman techniques, as well as Mass spectrometry (MS) and NMR well suited to yielding high quality chemical information for multi-component samples, requiring no a priori knowledge of the constituents (col. 6, lines 3-11).

Accordingly, at the effective filing date of the present application, it would have been obvious for an ordinary skilled artisan in the art to modify the teachings for

Lochhead et al. by also forming a truly integrated microanalysis device containing a biological material doped sol-gel suitable and interfacing with any analytical detection means well known in the art for chromatographic analysis of small and/or macromolecular and/or other solutes in the liquid phase in light of the teachings of Avnir et al and Swedberg et al discussed above.

An ordinary skilled artisan would have been motivated to carry out the above modification because while Lochhead et al. already teach the feasibility of fabricating micron-scale devices containing a biological material embedded in a sol-gel at least for sensor, waveguide and integrated optics applications, Avnir et al already dislose that doped sol gel glasses for all chromatographic purposes including liquid, gas and thin layer chromatography, and Swedberg et al teach a format of a microdevice containing sample separation means that include electochromatographic separations performed in columns or microcapillary format, that allows high throughput sample processing and analysis of small and/or macromolecular solutes in biological liquids in a truly integrated fashion. Lochhead et al also note that microfabriated devices are attractive for applications ranging from remote chemical sensing to medical analysis due to the potential of rapid analysis and portability.

An ordinary skilled artisan would have a reasonable expectation of success based on the teachings of Lochhead et al, Avnir et al, and Swedberg et al, as well a high level of skill of an ordinary skilled artisan in the art.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

Claim 44 is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Celine Qian, Ph.D., may be reached at (571) 272-0777, or SPE, Dave Nguyen, at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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DAVID GUZO
PRIMARY EXAMINER